PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
SPRV7PCT/P4422PC00		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/FI2005/000064	31.01.2005	30.01.2004

International Patent Classification (IPC) or national classification and IPC
INV. C07K16/06

Applicant
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1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 3 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☒	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06.06.2005	22.05.2006

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/FI2005/000064

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-18	as published

Claims, Numbers

1-17	filed with telefax on 27.04.2006

Drawings, Sheets

1/1	as published

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☒ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☒ the claims, Nos. 1-5, 17
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-17
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-17
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-17
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

SECTION V

2. CITATIONS AND EXPLANATIONS

2.1 Amended Claims 1 to 17 (filed by fax on 27.04.06) have their basis in the originally filed application, and therefore satisfy Article 34(2)(b)PCT.

2.2 The following documents have been considered for the purposes of this report:

D1: EP0413197
D2: WO99/64462 (also cited in the application)
D3: "Protein liquid Chromatography" Journal of Chromatography Library 2000, Vol. 61, Chapter 21, pages 766-768.
D4: WO03/100080
D5: Perosa, F. et al (1990) J. Immunological Methods **128**:9-16
D6: Troccoli, N.M. et al (1998) Biologicals **26**:321-329

2.3 The present application pertains to methods for manufacturing improved virus-safe immunoglobulin compositions suitable for pharmaceutic purposes, e.g. for parenteral administration.

Having regard to the experimental results provided in the supporting description, the inventive contribution of the present disclosure seems to be in the combination of particular sequential precipitation and nanofiltration steps, as defined in the newly filed independent Claims 1 and 11, which enable the desirable filtration of small virus particles and the manufacture of purified immunoglobulin preparations which are free from polymeric aggregates.

Procedural approaches comprising all the characterizing working steps defined in present independent Claims 1 and 11 are neither disclosed nor suggested by the available prior art (D1-D6). Accordingly the subject-matter presently claimed (cf Claims 1-17) would appear to satisfy the novelty and inventive step criteria set forth in

Article 33(2) and (3) PCT.

The subject-matter of Claims 1-17 also meets the requirement of industrial applicability pursuant to Article 33(4) PCT.

SECTION VII

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 and D3-D6 is not mentioned in the description, nor are these documents identified therein.

2. The description is not in conformity with the claims as required by Rule 5.1(a)(iii) PCT.

3. With respect to Claim 4 it is noted that the use of expressions like "preferably"(or "for example" or "such as"...) has no limiting effect on the scope of said claim, i.e. the feature(s) following such expressions is (are) to be regarded as entirely optional (cf PCT Guidelines, C-III, 4.6).

Claims

1. A process for preparing a purified, essentially virus-safe immunoglobulin preparation, said process comprising the steps of

a) subjecting a starting solution comprising immunoglobulin and polymeric proteins to at least one virus-inactivation step, in which the composition is contacted with caprylic acid to form a precipitate and a supernatant solution comprising dissolved immunoglobulin and polymeric proteins,

b) recovering the supernatant solution,

c) contacting the supernatant solution with at least one ion exchange resin to produce a first effluent comprising immunoglobulin,

d) recovering the first effluent,

e) subjecting the first effluent to nanofiltration on a filter having an average pore size of about 10 to 40 nm to remove any enveloped and non-enveloped viruses and to produce a second effluent,

f) recovering the second effluent, and

g) formulating it to a pharmaceutically acceptable, virus-safe immunoglobulin preparation, which is free from polymeric proteins,

wherein polymeric proteins are removed from the supernatant solution obtained from step b by adding polyethylene glycol to the supernatant solution.

2. The process according to claim 1, wherein step a is carried out by adding caprylic acid to a final concentration of 15 – 60 mmol/l, preferably to 20 – 50 mmol/l.caprylic acid.

3. The process according to claim 2, wherein step a is carried out at a pH of about 4.0 to 5.0.

4. The process according to any of claims 1 to 3, wherein the starting solution is provided by dissolving an immunoglobulin-containing blood fraction in an aqueous solution at a pH of about 4.0 to 5.0, preferably at 4.5 to 5.0.

5. The process according to any of claims 1 to 4, wherein the pH of the supernatant solution of step b is adjusted to a value of about 5.3 or higher.

14. The method according to claim 13, wherein the solution is filtered using a trans-membrane pressure of 0.5 to 5.5 bar.

15. The method according to any of claims 11 to 14, wherein at least 5 kg, preferably at least 7.5 kg, of immunoglobulin is passed through 1 m^2 of filter area with less than 50 % decrease in filter flux.

16. The method according to any of claims 11 to 15, wherein the immunoglobulin solution is filtered on a composite virus-removal filter.

17. The method according to any of claims 11 to 16, wherein filtration is carried out at a pH of about 4.2 to 4.8.